I know the patient has diabetes, but am I sure this is T2DM?

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Learning Objectives

- Use key items from the History, Physical Exam, and Laboratory tests to distinguish between T1 and T2DM
- List prevalence rates of type 1 and type 2 diabetes
- Compare and contrast the immediate and long term management of T1 vs. T2DM
- Know where to find a good review of this for reference

Outline

- Definition, and historical classification, of diabetes mellitus
- Classification
- “Type 1” vs “Type 2”
  - Epidemiology
  - History
  - Physical exam
  - Laboratory results
  - Management
- Cases

Definition of Diabetes Mellitus

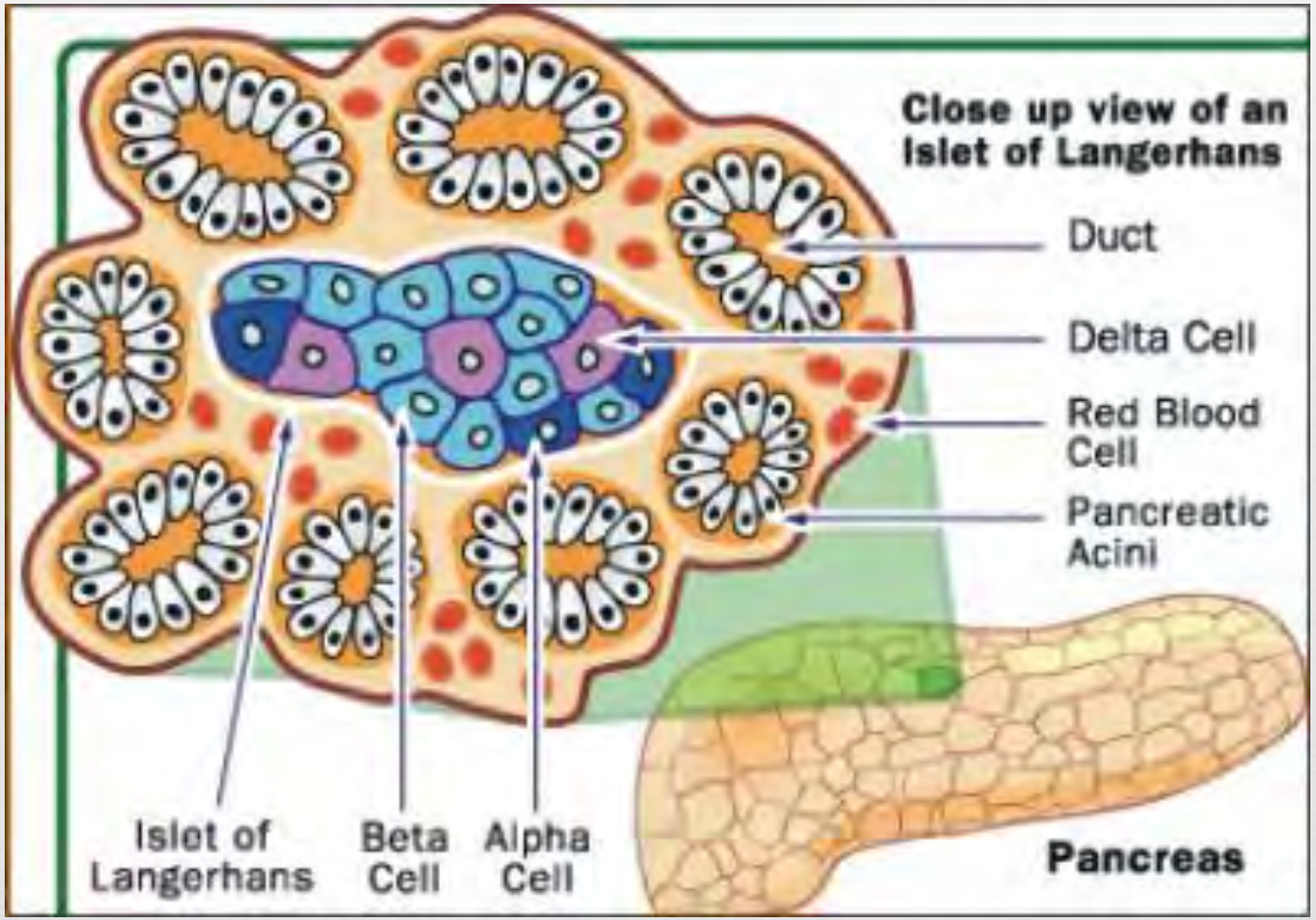
What is Diabetes Mellitus?

- a **metabolic** disorder characterized by the presence of **hyperglycemia** due to defective insulin secretion, defective insulin action or both

Classification

- A classification… is a construct – or paradigm - that encapsulates current scientific understanding of a disease, and offers guidance as to how this might translate into clinical practice. Based as it is upon incomplete knowledge and understanding, any such formulation can only be provisional, and this will apply with particular force to a condition such as diabetes whose causes are largely unknown.

Pancreas structure & function



Counter-regulatory Hormones

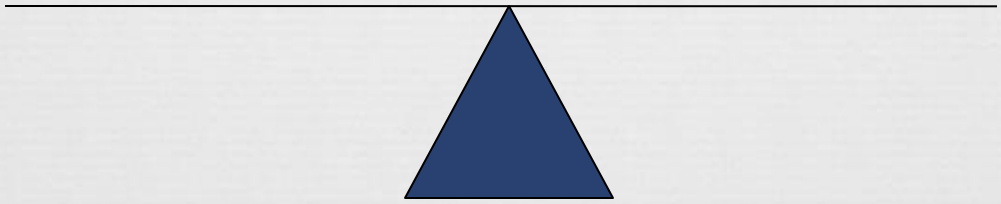
INSULIN

GLUCAGON

CATECHOLAMINES

CORTISOL

GROWTH HORMONE



Historical evolution

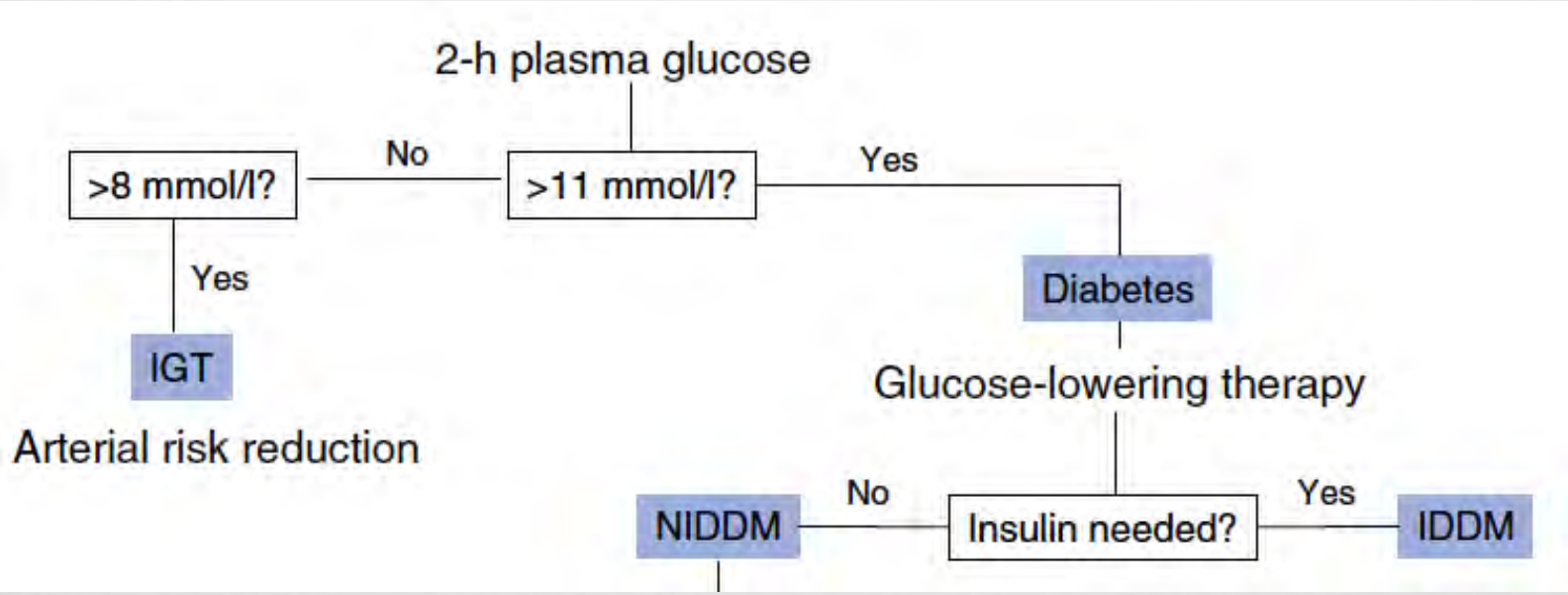
- Diabetes as one disease
- "orphan observation:" a fact that does not fit and is therefore ignored; until it is reconciled with previous knowledge, at which point the paradigm shifts
  - young, thin, depended on insulin to survive vs. older, could survive without insulin
  - insulin-sensitive vs. insulin-insensitive (Himsworth 1936)
- 1951: first use of the terms T1 and T2DM

Historical evolution

- 1951: first use of the terms T1 and T2DM
- linking of central obesity to insulin resistance, hypertension and arterial disease
- heterogeneity of diabetes only accepted once concept of autoimmunity was developed: detection of islet cell Ab, HLA associations
- paradigm of lumping into one category quickly abandoned… too quickly?

Historical evolution

- 1980: WHO report endorsed the division, also subdivided into groups based on vascular risk (diabetes vs. impaired glucose tolerance); treatment driven classification



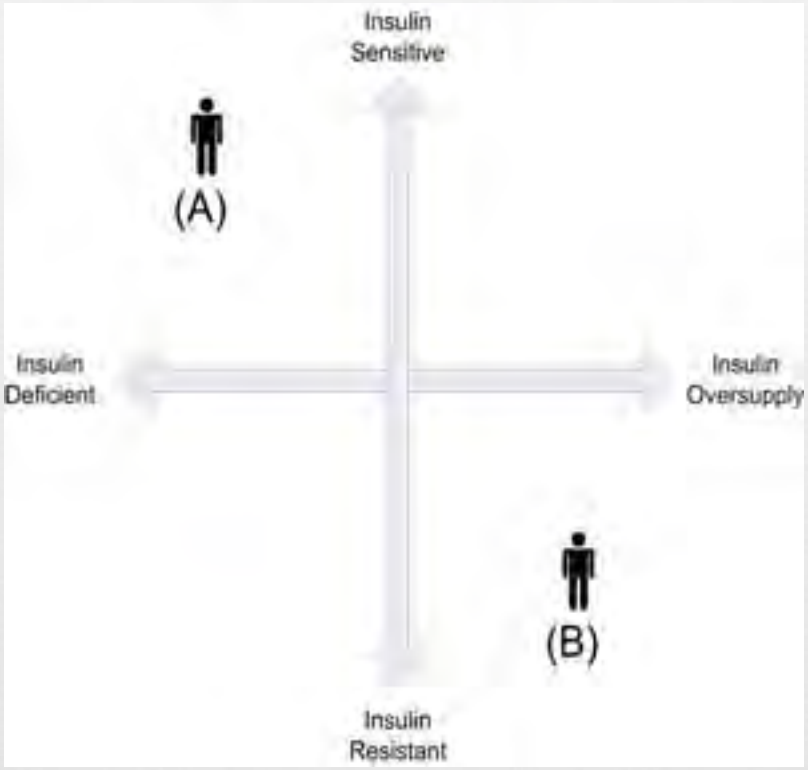
Historical evolution

- 1997: American Diabetes Association (ADA) argued that classification based on therapy was not satisfactory
  - widespread trend towards earlier use of insulin in T2DM
- based on the presence or absence of useful residual insulin secretions: T1 insulin deficiency, T2 functional category (ongoing insulin secretion, exclusion of other known types of DM, absence of hallmarks of T1)
  - C-peptide level

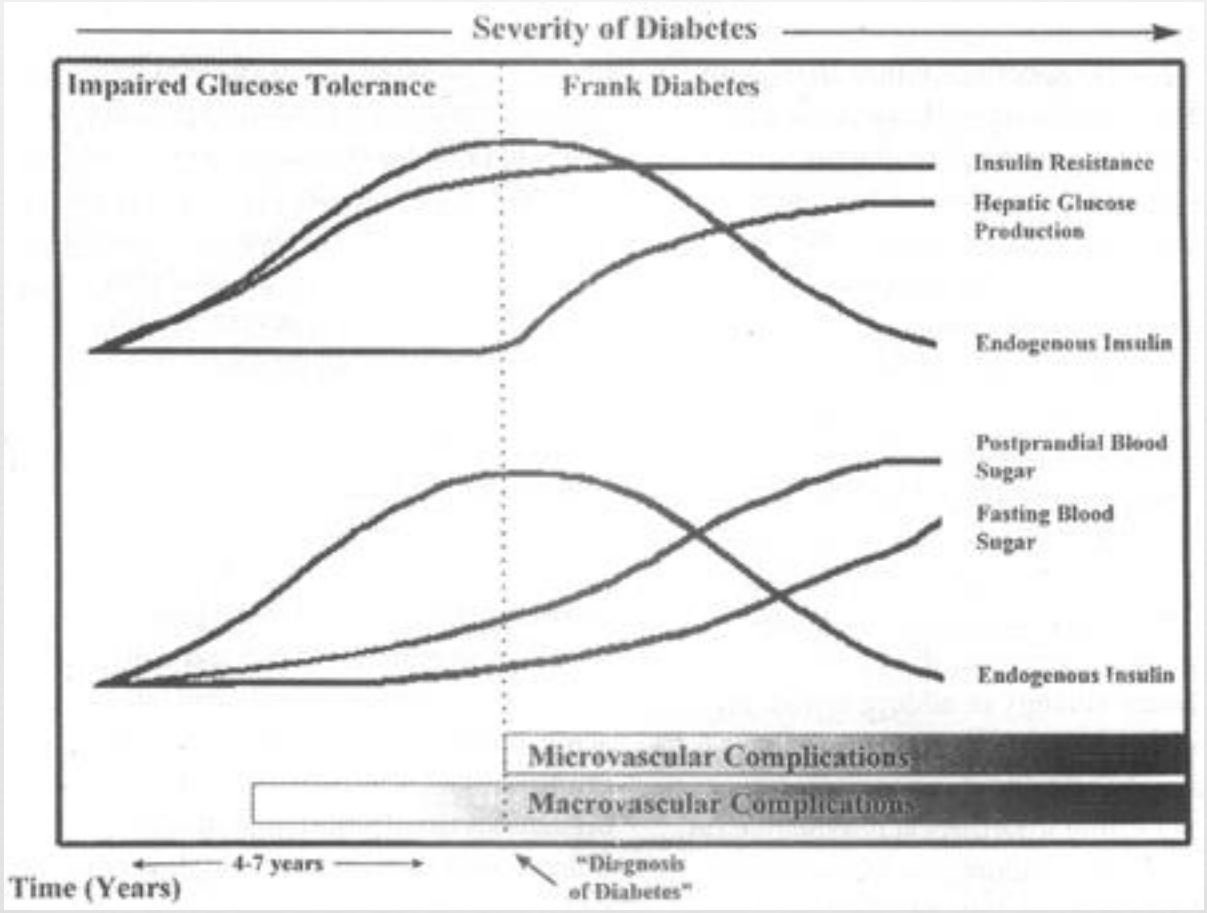
Historical evolution

- what about…
  - ketosis prone T2DM in adult African-Americans ("flatbush diabetes")?
  - T1DM in obese youth ("double diabetes")?

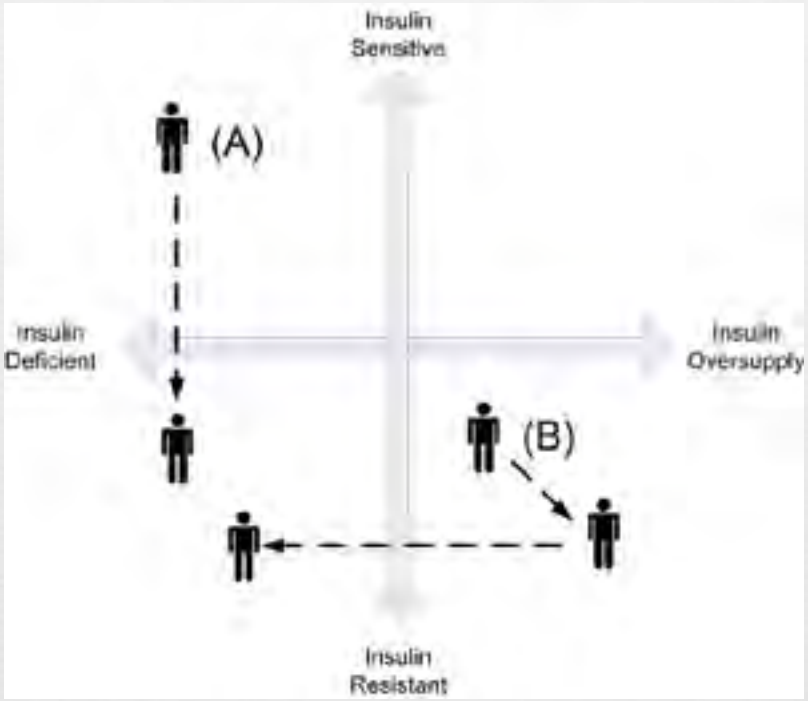
Continuum


Insulin
Sensitive
(A)
Insulin
Deficient
Insulin
Oversupply
(B)
Insulin
Resistant

Natural history of T2DM



Continuum


Insulin
Sensitive
(A)
Insulin
Deficient
Insulin
Oversupply
(B)
Insulin
Resistant

Diagnosis of Diabetes Mellitus

Criteria for the Diagnosis of Diabetes

Table 2
Diagnosis of diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
A1C ≥6.5% (in adults)
Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes (see text)
or
2hPG in a 75 g OGTT ≥11.1 mmol/L
or
Random PG ≥11.1 mmol/L
Random = any time of the day, without regard to the interval since the last meal

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Prediabetes: IFG, IGT, Increased A1C

Table 4
Diagnosis of prediabetes

Test	Result	Prediabetes category
FPG (mmol/L)	6.1–6.9	IFG
2hPG in a 75 g OGTT (mmol/L)	7.8–11.0	IGT
A1C (%)	6.0–6.4	Prediabetes

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test.

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Classification of Diabetes Mellitus

Classification

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Gestational diabetes mellitus
- Other specific types

Classification - CDA

- Type 1 diabetes:
  - DM that is primarily a result of **pancreatic beta cell destruction** and is prone to ketoacidosis; autoimmune process or unknown etiology of beta cell destruction
- Type 2 diabetes:
  - may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance
- Gestational diabetes mellitus:
  - glucose intolerance with onset or first recognition during **pregnancy**

Appendix 1 – CDA guidelines

Type 1 diabetes mellitus
Beta cell destruction, usually leading to absolute insulin deficiency
- Immune-mediated
- Idiopathic

Type 2 diabetes mellitus
May range from predominant insulin resistance with relative insulin deficiency to predominant secretory defect with insulin resistance

Gestational diabetes mellitus
Onset or first recognition of glucose intolerance during pregnancy

Other specific types

Genetic defects of beta cell function
- Chromosome 20, HNF-4alpha (formerly MODY1)
- Chromosome 7, glucokinase (formerly MODY2)
- Chromosome 12, HNF-1alpha (formerly MODY3)
- Chromosome 13, IPF-1 (formerly MODY4)
- Chromosome 17, HNF-1beta (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Mitochondrial DNA
- Neonatal diabetes (e.g. due to Kir6.2 mutation)
- Others

Genetic defects in insulin action
- Leprechaunism
- Lipoatrophic diabetes
- Rabson-Mendenhall syndrome
- Type A insulin resistance
- Others

Diseases of the pancreas
- Cystic fibrosis
- Fibrocalculous pancreatopathy
- Hemochromatosis
- Neoplasia
- Pancreatitis
- Trauma/pancreatectomy
- Others

Endocrinopathies
- Acromegaly
- Aldosteronoma
- Cushing syndrome
- Glucagonoma
- Hyperthyroidism
- Pheochromocytoma
- Somatostatinoma
- Others

Infections
- Congenital rubella
- Cytomegalovirus
- Others

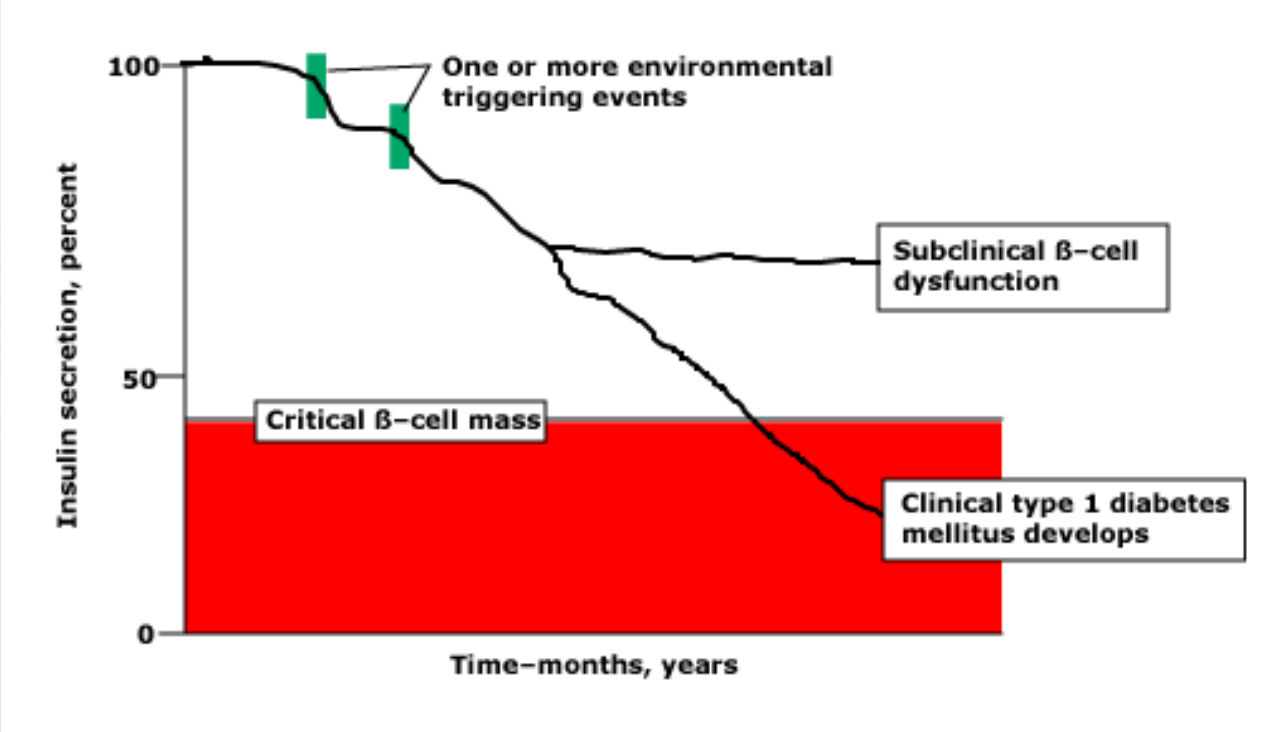
Uncommon forms of immune-mediated diabetes
- Anti-insulin receptor antibodies
- "Stiff-man" syndrome
- Others

Drug- or chemical-induced
- Atypical antipsychotics
- Beta-adrenergic agonists
- Cyclosporine
- Diazoxide
- Glucocorticoids
- Interferon alfa
- Nicotinic acid
- Pentamidine
- Phenytoin
- Protease inhibitors
- Thiazide diuretics
- Thyroid hormone
- Others

Other genetic syndromes sometimes associated with diabetes
- Down syndrome
- Friedreich ataxia
- Huntington chorea
- Klinefelter syndrome
- Laurence-Moon-Bardet-Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Turner syndrome
- Wolfram syndrome
- Others

Type 1 vs Type 2

Pathophysiology of Type 1 diabetes



Graph obtained from UptoDate.com: Diabetes mellitus type 1.

Pathophysiology of type 2 diabetes

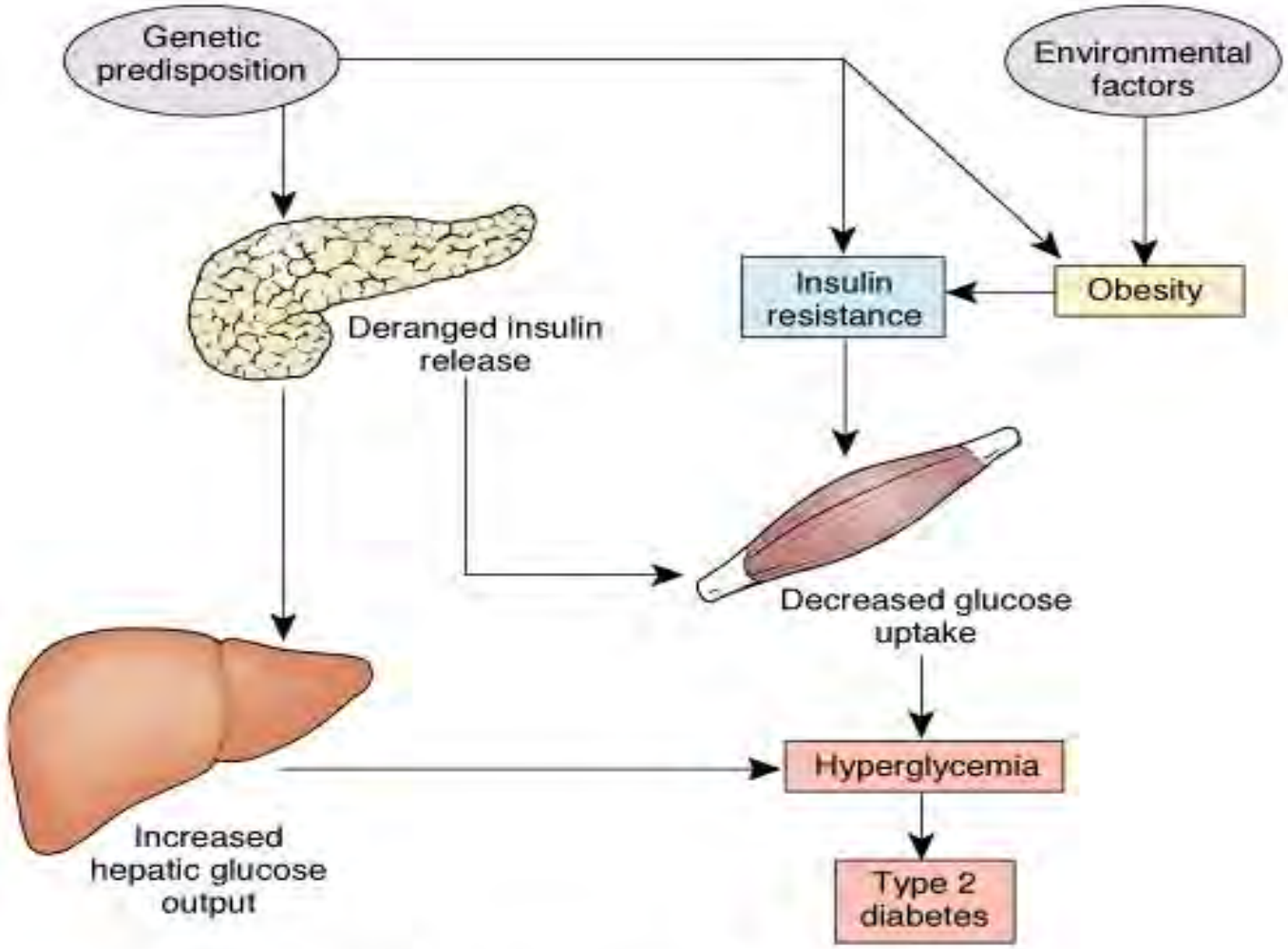


Figure 43-7 Pathogenesis of type 2 diabetes mellitus.

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Onset		
Etiology		
Ethnicity		
Genetics		
Pathophysiology		
Natural Hx		
Body Habitus		
Circulating antibodies		
Screening		
Risk factors		

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Onset	< 30 years of age	> 40 years ?
Etiology	Autoimmune/unknown	Complex & multifactorial
Ethnicity	Caucasians	Black, Hispanic, Aboriginal, Asian ethnicity
Genetics	Monozygotic concordance 30-40% Associated with HLA class II DR3, DR4 (in up to 95% of patients); also DQ, DB	Monozygotic concordance 70-90%: greater heritability Polygenic Non-HLA associated

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Patho-physiology	Genetic + immune + environmental factors = β-cell destruction Autoimmune process ?triggered by environmental factors Pancreatic cells infiltrated with lymphocytes = islet cell destruction 80% of β-cell mass destroyed before T1 features present	Impaired insulin secretion Peripheral insulin resistance (likely due to R and post-R abnormalities) Excess hepatic glucose production
Natural Hx	After initial presentation, can have honeymoon period – residual cells still produce sufficient insulin once BG controlled Eventual complete insulin deficiency	Early on, BG remains normal despite insulin resistance as β-cells compensate with ↑ insulin production As insulin resistance & compensatory hyperinsulinism continue, β-cells unable to maintain hyperinsulinema

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Presentation	Abrupt onset Severe hyperglycemias Ketosis	Insidious onset Mild-moderate hyperglycemias No ketosis
	DKA (25%) Polyuria, polydipsia, weight loss	Asymptomatic Screening BW Polyuria, polydipsia HHS (rare)
Confusing cases	Initially not dependent on insulin but slowly develop autoimmune mediated insulin deficiency later (LADA) Longer duration of symptoms in adults vs children Overweight or obese +/- signs of insulin resistance Present after age 35 (25%)	DKA (rare; particular ethnic groups, or high counter-reg H)

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Acute complications	DKA	HHS (hyperosmolar hyperglycemic state)*
Body Habitus	lean to wasted	typically overweight, central obesity
Circulating antibodies	Islet cell Ab: present in 60-85%; most common islet cell Ab is anti-GAD (glutamic acid decarboxylase) Up to 60% have Ab against insulin	< 10%
Other labs	low C-peptide after months of stabilization	

Comparison: Type 1 vs Type 2

	Type 1	Type 2
Risk factors	Personal history of other autoimmune diseases: • thyroid disease • myasthenia gravis • pernicious anemia Family history of T1DM	• Age ≥40 • First degree relative with T2DM • Member of high risk ethnicity • History of IGT or IFG • Presence of complications associated with DM • Vascular disease • History of GDM • History of delivery of a macrosomic infant • Hypertension • Dyslipidemia • Abdominal obesity • PCOS • Schizophrenia • Acanthosis nigricans
Screening	Subclinical prodrome can be detected in 1st and 2nd degree relatives by presence of auto-antibodies	• q3 years if age >40 • earlier if risk factors • pregnancy • classic symptoms or complications

Table 1
Risk factors for type 2 diabetes

- Age ≥40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g. Aboriginal, African, Asian, Hispanic or South Asian descent)
- History of prediabetes (IGT, IFG or A1C 6.0%–6.4%)*
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Presence of end organ damage associated with diabetes:
  - Microvascular (retinopathy, neuropathy, nephropathy)
  - Macrovascular (coronary, cerebrovascular, peripheral)
- Presence of vascular risk factors:
  - HDL cholesterol level <1.0 mmol/L in males, <1.3 mmol/L in females*
  - Triglycerides ≥1.7 mmol/L*
  - Hypertension*
  - Overweight*
  - Abdominal obesity*
- Presence of associated diseases:
  - Polycystic ovary syndrome*
  - Acanthosis nigricans*
  - Psychiatric disorders (bipolar disorder, depression, schizophrenia†)
  - HIV infection‡
  - OSA§
- Use of drugs associated with diabetes:
  - Glucocorticoids
  - Atypical antipsychotics
  - HAART‡
  - Other (see Appendix 1)
- Other secondary causes (see Appendix 1)

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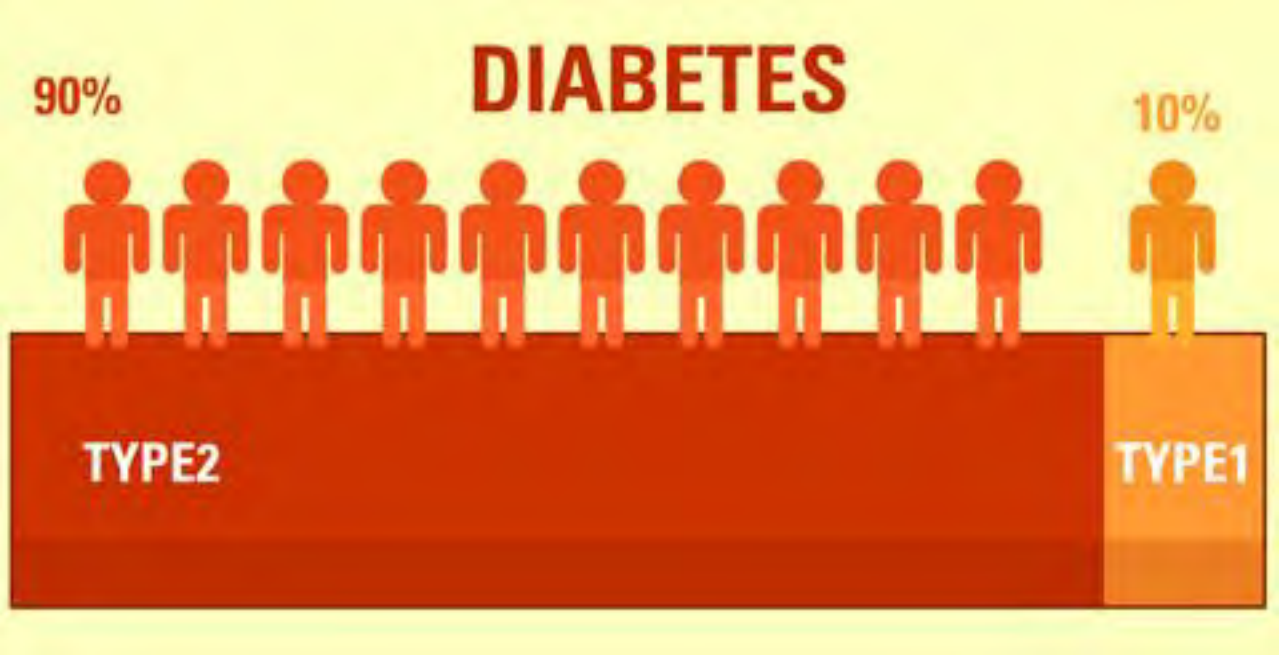
Prevalence



Management of DM

Lifestyle for all

- Nutrition
- Exercise
- Weight loss if overweight

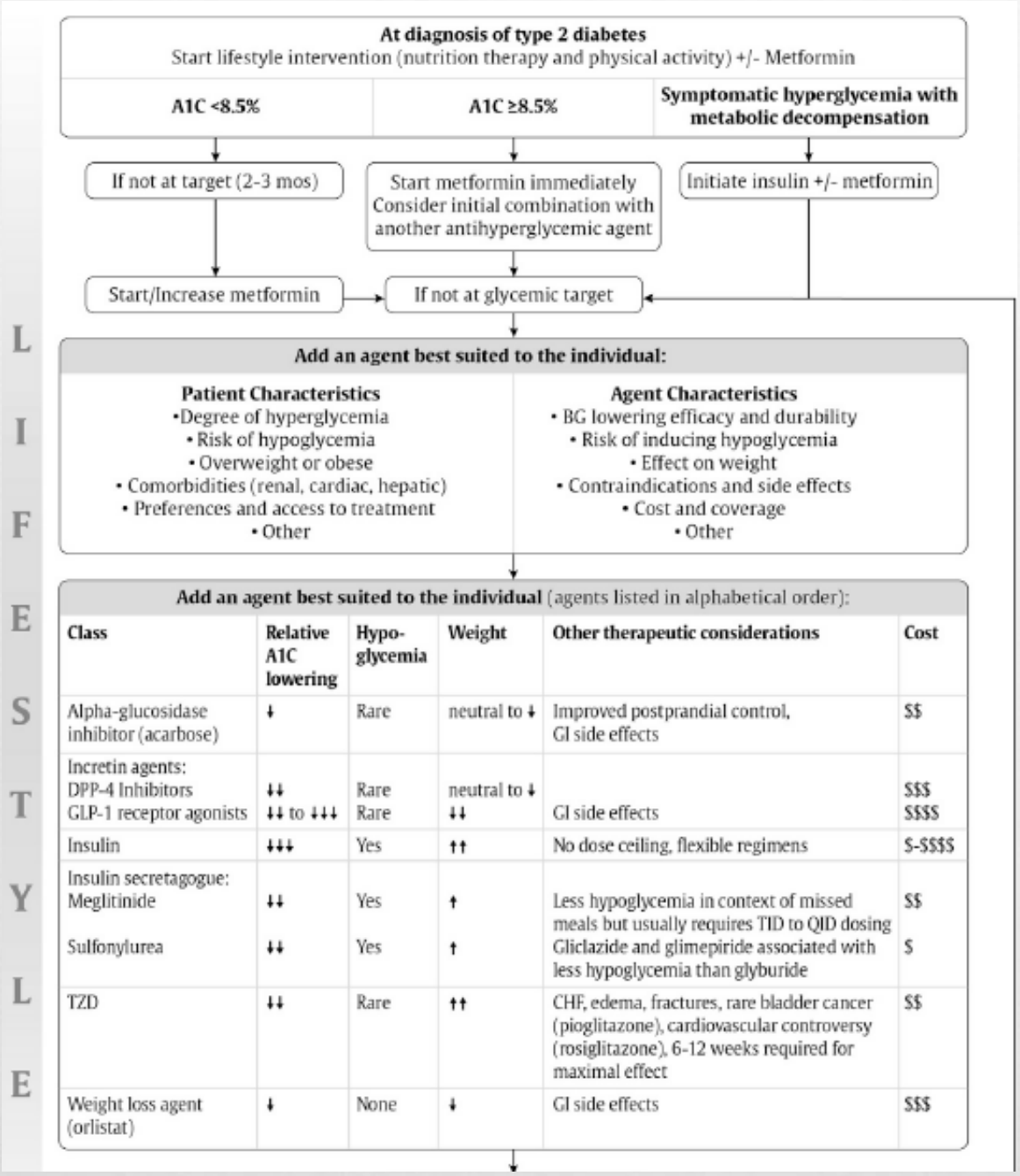
Management of T1DM

Table 1
Types of insulin

Insulin type (trade name)	Onset	Peak	Duration
Bolus (prandial) insulins			
Rapid-acting insulin analogues (clear)			
Insulin aspart (NovoRapid®)	10–15 min	1–1.5 h	3–5 h
Insulin glulisine (Apidra®)	10–15 min	1–1.5 h	3–5 h
Insulin lispro (Humalog®)	10–15 min	1–2 h	3.5–4.75 h
Short-acting insulins (clear)			
Humulin®-R	30 min	2–3 h	6.5 h
Novolin® ge Toronto			
			24 h, detemir 16–24 h)
Premixed insulins			
Premixed regular insulin–NPH (cloudy)	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Humulin® 30/70			
Novolin® ge 30/70, 40/60, 50/50			
Premixed insulin analogues (cloudy)			
Biphasic insulin aspart (NovoMix® 30)			
Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)			

INSULIN

Management of T2DM



Choice of therapy

- insulin is never wrong
  - does require teaching on how to care for and use insulin; prevention, recognition and treatment of hypoglycemia; adjustments for food intake (e.g. carbohydrate counting) and physical activity, and self-monitoring of blood glucose (SMBG).
  - rapidly normalizes hyperglycemia (may result in better long 1 year control and/or remission)

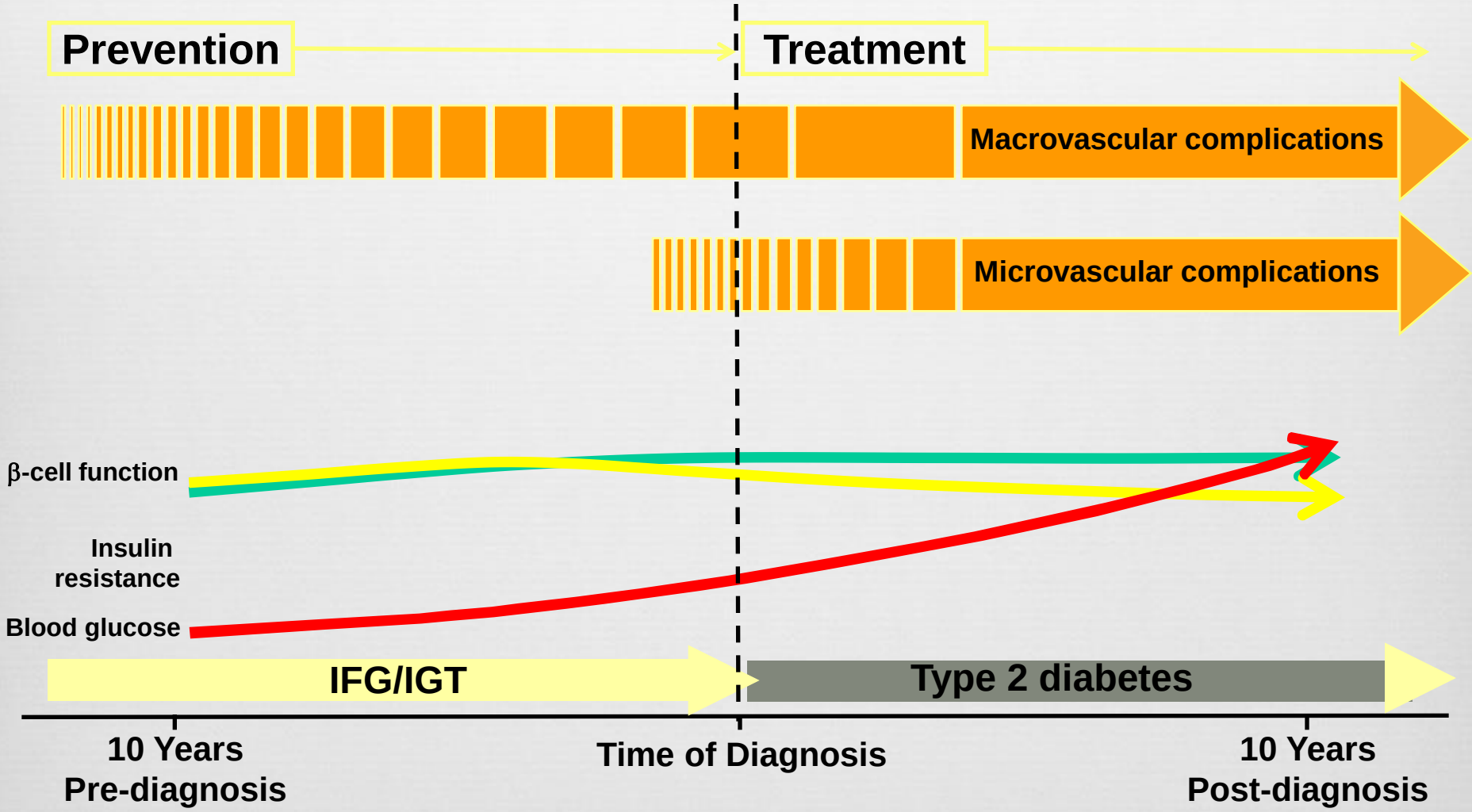
66. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371: 1753–60

Choice of therapy

- Given the risk of DKA, consider insulin as initial therapy in patients who:
  - A1C >10%
  - fasting BG >14
  - random BG >16
  - ketonuria
  - unplanned weight loss with hyperglycemia

Long-term Management

Pathophysiology of Type 2 Diabetes and Progression Over Time



IFG = impaired fasting glucose; IGT = impaired glucose tolerance.
Adapted from: DeFronzo RA. Med Clin N Am 2004; 88:787-835.

Monitoring in DM

Intervention	Frequency	Notes
History and physical examination		
Smoking cessation counseling	Every visit	For smokers only
Blood pressure	Every visit	**Goal <130/80**
Dilated eye examination	Annually*	onset T2DM, 3-5y after T1DM
Foot examination	Annually	q visit if PVD or neuropathy
Sexual health inventory	Regularly	adult men, SHIM, onset T2DM
Laboratory studies		
Fasting lipid profile	Annually	q two years if profile low risk
A1C	q3-6 months	Goal <7%
Microalbuminuria	Annually	onset T2DM, 3-5y after T1DM
Serum creatinine	Initially	as indicated
Vaccinations		
Pneumococcus	One time	
Influenza	Annually	
Education, self management	Annually	

Cases

Case

27 year old male is brought to the ER by ambulance. His mother found him in a semi-conscious state at his desk studying for his exams. She informs the paramedics that for the last 2 weeks her son has been “constantly going to the bathroom”, and is persistently thirsty. He has lost about 10 lbs despite eating normally.

The triage nurse does a CBGM and the reading is “hi”. He is hyperventilating and has “fruity breath”. He complains of abdominal pain.

Labs

- Glucose 24 mmol/L
- Na+ 131
- K+ 4.0
- Cl 101
- HCO3 9
- pH 7.1

Does he have DKA?

- Criteria:
- arterial pH ≤7.3
- serum bicarbonate ≤15 mmol/L
- anion gap >12 mmol/L
- positive serum and/or urine ketones
- glucose usually ≥14.0 mmol/L, but can be lower

Precipitating factors

- Inadequate insulin
  - new onset diabetes, noncompliance
- Infection
- Infarction - MI
- Intoxication/drugs – glucocorticoids, etc
- Ischemia - CVA

Case 2

- 24 year old man presents to the emergency room complaining of polyuria, polydipsia, weight loss, and blurry vision
- Medicine is consulted because he is found to have a BG of 28 mmol/L

- Does he have diabetes?

- What further information do you want to help you determine if he is insulin deficient or insulin resistant (Type 1 vs Type 2)?

History

- type of fluid to quench thirst? – apple juice
- PMH – no autoimmune disorders
- FHx – mother, sister has diabetes; no autoimmune
- SHx – smoking, EtOH, drugs - no

Physical exam

- Ethnicity – East Indian
- BP – 140/90
- BMI - 29
- central obesity – waist circumference 102 cm
- Acanthosis nigricans – yes on neck
- Thyroid exam - normal

Labs

- fasting BG – 28 mmol/L
- Hb A1C – 16 %
- bicarb, anion gap, serum/urine ketones - normal
- fasting lipids – triglycerides, LDL high, HDL low

Case

- What type of diabetes does he have?
- How would you initally treat him?

Questions?

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Questions?